Attorney's Docket No.: 10276-015002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Myra A. Lipes et al. Art Unit : 1632
Serial No. : 09/770,601 Examiner : Anne-Marie Baker
Filed : January 26, 2001
Title : IMMUNOLOGICALLY PRIVILEGED CELLS AND USES THEREOF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132 OF DR. MYRA LIPES

I, Myra Lipes, a permanent resident of the United States, residing in Brookline, MA, hereby declare as follows:

1. I am an Investigator at Joslin Diabetes Center, Assistant Professor of Medicine at Harvard Medical School, and a Board certified pediatric endocrinologist. I also am Co-Director of the Manipulated NOD Core, JDRF Center on Immunological Tolerance at Harvard Medical School. I received my M.D. degree from McGill University Faculty of Medicine, Montreal, Canada in 1981. I have over 20 years of research and clinical experience in immunology and endocrinology and am an expert in the field of beta cell autoimmunity and diabetes.

2. I am a co-inventor of the patent application referenced above.

3. I have been advised and understand that the Examiner has rejected claims 27, 30-31, 60-61, 64-74, 79-83 and 86 of the above-referenced application, which are directed to methods of producing insulin in a subject in vivo. The methods include introducing into a subject an

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I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

4/9/04
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Myra Lipes
Signature

Myra Lipes
Typed or Printed Name of Person Signing Certificate

intermediate lobe (IL) pituitary cell that has been genetically engineered to express insulin. The Examiner has rejected the claims based on lack of written description and enablement.

4. The Examiner states that: "one of skill in the art could not envision the entire genus of promoters that are active in IL cells." This is not correct. In view of what was known at the time of priority, a skilled person could readily envision the entire class of promoters that are active in IL cells. The knowledge and skill in the art necessary to select a promoter to express a protein in any one particular cell type was extremely high. It was a routine and established procedure in the art at the time of filing to use, e.g., a constitutive promoter or a promoter specific to the relevant cell type. Both constitutive promoters and promoters specific to IL cells were known in the art, can work in the claimed methods, and representative examples are disclosed in the specification. See page 14, lines 5-13, of the specification, where, in addition to the POMC promoter, a representative number of constitutive promoters, such as the CMV and SV-40 early promoters, are disclosed. Note that at page 27, lines 29-32, of the specification, it is shown that CMV promoter directs expression in IL cells. Other constitutive promoters that were routinely used in the art at the time of filing include the JC polymovirus promoter, and the chicken beta-actin promoter. In addition, IL-specific promoters besides POMC promoter were known, such as the prodynorphin (proDyn) promoter. See, e.g., Naranjo et al. (1991, Neuron 6(4):607-17), describing the proDyn promoter, and Day et al. (1993, Endocrinology 133:2652-2659), describing proDyn gene expression in IL cells. Therefore, a skilled person would have been able to envision the entire class of promoters that are active in IL cells.

5. The Examiner also states that the specification "fails to provide an enabling disclosure for the use of transgene constructs that . . . . do not include the POMC promoter because the proper regulation of insulin secretion is critical for successfully carrying out the claimed method." This statement seems to be based on the Examiner's erroneous belief that the (pro-opiomelanocortin) POMC promoter is glucose-regulated. In fact, the POMC promoter is not glucose sensitive. The experiments described in the specification show that IL cells have the proper prohormone processing machinery to produce and secrete fully processed, mature insulin sufficient to produce a therapeutic effect in a diabetic subject even in the absence of insulin

secretion being tightly coupled to serum glucose concentrations. See, for example, the section bridging pages 25 and 26 of the specification, which shows that transplantation of insulin-producing IL cells under the kidney capsule of spontaneously diabetic NOD mice resulted in a significant gain in body weight, complete remission from diabetic symptoms, a return to near-normoglycemia, and insulin levels in a similar range to random insulin levels of non-diabetic control mice. There is absolutely no reason to think that other promoters, including other IL-specific promoters or constitutive promoters, would not work also. Therefore, the claimed methods can be carried out even without a glucose-sensitive promoter. Although the ideal or perfect insulin secreting cell would be glucose-sensitive, this does not mean that there is no place for insulin production that is not regulated by glucose levels. Secretion of basal levels of insulin also provides therapeutic benefit, e.g., by reducing risk of ketoacidosis that results from absolute insulin deficiency that occurs with Type I diabetes. Furthermore, even the standard treatment for diabetes, the self-administration of exogenous recombinant insulin, is not free of risk of episodes of hypoglycemia or hyperglycemia.

6. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title XVIII of the United States Code, and that such willful false statements may jeopardize the validity of this Application for Patent or any patent issuing thereon.

Myra Lipes

Myra Lipes, M.D.

4/9/04

Date

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